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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,476	09/30/2003	Robert B. DuBridge	181 US UT01	7526

47470 7590 02/21/2006

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 02/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/676,476	DUBRIDGE, ROBERT B.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 2-26 and 30-65 is/are pending in the application.

4a) Of the above claim(s) 20-26 and 30-65 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 2-19 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 30 September 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 11/29/2005, in which claims 1 and 27-29 were canceled; and claims 2-8, 10-12 and 16 were amended. Currently, claims 2-26 and 30-65 are pending. Applicants' arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Applicant elected Group I (claims 1-19 and 27-29) without traverse in the reply filed 3/18/2005. Applicant confirmed the provisional election of Flp recombinase as the species of recombinase in the reply filed 11/29/2005.

Claims 20-26 and 30-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/18/2005.

Claims 2-19 are under consideration.

Response to Arguments - 35 USC § 112

The previous rejection of claims 7, 10, 12, 16 and 28 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention has been withdrawn in view of Applicant's amendment.

Response to Arguments - 35 USC § 102

The rejection of claims 1, 4, 5 and 27 under 35 U.S.C. 102(b) as being anticipated by Bode et al has been withdrawn in view of Applicant's amendment.

The rejection of claims 1, 4, 5, 8 and 27 under 35 U.S.C. 102(b) as being anticipated by Seibler et al has been withdrawn in view of Applicant's amendment.

The rejection of claims 1-3, 5, 8 and 27 under 35 U.S.C. 102(e) as being anticipated by Ow has been withdrawn in view of Applicant's amendment.

The rejection of claims 27-29 under 35 U.S.C. 102(e) as being anticipated by Cheo et al has been withdrawn in view of Applicant's amendment.

Claim Rejections - 35 USC § 103

Claims 4-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheo et al (US Patent Application Publication No. 2002/0007051; see the entire reference) in view of Seibler et al (Biochemistry, Vol. 36, pages 1740-1747, 1997; see the entire reference). This rejection was made in the Office action mailed 6/1/2005 and has been altered to address Applicant's amendment to the claims in the reply filed 11/29/2005.

Regarding claim 11, Cheo et al teach an integration cassette (e.g. starting molecule or Destination vector) comprising two recombination sites flanking promoters, selectable markers, and tags such histidine tags or green fluorescent protein (e.g. paragraphs [0045], [0050], [0147],

[0148], [208] and [0488]; Figure 6). Further, Cheo et al teach the addition of regions that allow integration into eukaryotic chromosomes (e.g. transposable elements) (e.g. paragraph [0327]). Cheo et al teach a first target cassette comprising a polynucleotide to be substituted into the integration cassette flanked by two recombination sites (e.g. paragraphs [0045] and [0075]). Regarding the recombination sites and additional vectors, Cheo et al teach the following:

> In another specific aspect, the invention provides a method of cloning comprising providing at least a first nucleic acid molecule comprising at least a first and a second recombination site and at least a second nucleic acid molecule comprising at least a third and a fourth recombination site, wherein none of the first, second, third or fourth recombination sites is capable of recombining with any of the other sites, providing one or more vectors (e.g., two, three, four, five, seven, ten, twelve, etc.), comprising at least a fifth, sixth, seventh and eighth recombination site, wherein each of the fifth, sixth, seventh and eighth recombination sites are capable of recombining with one of the first, second, third or fourth recombination site, and conducting a recombination reaction such that at least said first and second molecules are recombined into said vectors. See paragraph [0154].

See also Figures 6 and 7 and paragraph [0075], for example. Further, Cheo et al teach a recombinase activity capable of recognizing the recombinase recognition sites of the second integration cassette and second target cassette (e.g. paragraphs [0055], [0196], [0253] and [0295]).

Regarding claim 4, Cheo et al teach the use of the Flp recombinase protein to catalyze recombination between Frt sites (e.g. paragraphs [0047], [0048], [0055] and [0253]). Cheo et al do not teach a rec element encoding the Flp recombinase activity.

Regarding claim 5, Cheo et al teach the use of mammalian cells, yeast cells and bacterial cells (e.g. paragraph [0436]).

Regarding claim 6, Cheo et al teach the use of a first integration cassette comprising two, three, four etc. open reading frames that further comprise sequences that function as internal

ribosome entry sites (IRES) (e.g. paragraph [0147]). The IRES allows the expression of two structural genes from a single transcript (i.e. bi-cistronic element) (e.g. paragraph [0544]).

Regarding claim 7, Cheo et al teach the use of a first integration cassette comprising a gene encoding a fusion protein comprising an N- or C-terminal tag such as an epitope tag or a six histidine tag (e.g. paragraph [0062]).

Regarding claim 8, Cheo et al teach a first target cassette comprising a first target gene and a first selectable marker gene that may be the same or different marker as compared to a selectable marker in the first integration cassette (e.g. paragraphs [0046] and [0148]).

Regarding claim 9, Cheo et al teach a first target cassette further comprising a plolycistronic element by including an IRES sequence to permit the bi-cistronic expression of two gene products from a single promoter (e.g. paragraphs [0143] and [0544]).

Regarding claim 10, Cheo et al teach the use of tagged proteins such as his tags (e.g. paragraph [0034]). Further, Cheo et al teach the use of recombination sites that comprise att sites, which comprise a TAG nucleic acid sequence (e.g. paragraph [0049]).

Regarding claim 12, Cheo et al teach the use of a second integration cassette comprising a gene encoding a fusion protein comprising an N- or C-terminal tag such as an epitope tag or a six histidine tag (e.g. paragraph [0062]).

Regarding claim 13, Cheo et al teach the use of a second integration cassette comprising two, three, four etc. open reading frames that further comprise sequences that function as internal ribosome entry sites (IRES) (e.g. paragraph [0147]). The IRES allows the expression of two structural genes from a single transcript (i.e. bi-cistronic element) (e.g. paragraph [0544]).

Regarding claim 14, Cheo et al teach a second target cassette comprising a first target gene and a first selectable marker gene that may be the same or different marker as compared to a selectable marker in the second integration cassette (e.g. paragraphs [0046] and [0148]).

Regarding claim 15, Cheo et al teach a second target cassette further comprising a plolycistronic element by including an IRES sequence to permit the bi-cistronic expression of two gene products from a single promoter (e.g. paragraphs [0143] and [0544]).

Regarding claim 16, Cheo et al teach the use of tagged proteins such as his tags (e.g. paragraph [0034]). Further, Cheo et al teach the use of recombination sites that comprise att sites, which comprise a TAG nucleic acid sequence (e.g. paragraph [0049]).

Regarding claim 17, Cheo et al teach the use of the system of claim 11 (described above) to construct nucleic acid molecules which encode more than one subunit of a multi-subunit complex such as an enzyme (e.g. paragraphs [0168] and [0354]).

Regarding claim 18, Cheo et al teach the use of the system of claim 11 (described above) to construct a multi-subunit complex that comprises an antibody molecule (e.g. paragraph [0168]).

Regarding claim 19, the recombination sites of the vectors function as "cloning sites" to clone recombinant molecules. Further, Cheo et al teach the inclusion of one or more restriction sites (e.g. multiple cloning sites) in the nucleic acid cassettes of the invention (e.g. paragraph [0140]).

Cheo et al do not teach a rec element encoding at least one recombinase activity that recognizes the recombinase recognition sites of the first integration cassette and second integration cassette or a rec element encoding flp recombinase activity.

Seibler et al teach a rec element, plasmid pOG44, encoding flp recombinase activity (e.g. page 1741, *(d) Recombination Prior to Integration*). Seibler et al teach that mammalian cells are capable of supporting recombinase mediated cassette exchange (RMCE) (as described in the rejection under 35 U.S.C. § 102(b) on pages 5-7 of the Office action mailed 6/1/2006), which will provide advantages including the ability to create reference integration sites characterized by their expression potential and long-term stability (e.g. page 1747, left column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Cheo et al with regard to cellular expression system capable of performing site-specific recombinase mediated cassette exchange to include the rec element encoding flp recombinase taught by Seibler et al because Cheo et al teach it is within the ordinary skill in the art to perform recombination reactions *in vivo* in mammalian cells and Seibler et al teach the use of flp recombinase activity encoded by a plasmid to mediate site-specific recombination reactions *in vivo* in mammalian cells.

One would have been motivated to make such a modification in order to receive the expected benefit of identifying reference integration sites in the mammalian genome for reproducible levels of expression as taught by Seibler et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 4-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheo et al (US Patent Application Publication No. 2002/0007051; see the entire reference) in view of Cox et al (US Patent No. 6,140,129; see the entire reference). This rejection has been included to address embodiments not covered by the combination of references set forth above. This rejection was made in the Office action mailed 6/1/2006 and has been altered to address Applicant's amendment to the claims in the reply filed 1/29/2005.

The teachings of Cheo et al are described in the above rejection and are applied as before.

Cheo et al do not teach a rec element encoding at least one recombinase activity that recognizes the recombinase recognition sites of the first integration cassette and second integration cassette, or a rec element encoding flp recombinase activity.

Cox et al teach a rec element encoding flp recombinase activity for expression in bacteria (e.g. column 6, lines 38-43). Further, the FLP system of Cox et al provides a method that can regulate recombination events and introduce FRT targets virtually anywhere in the chromosome (e.g. column 2, lines 6-14).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Cheo et al with regard to cellular expression system capable of performing site-specific recombinase mediated cassette exchange to include the rec element encoding flp recombinase taught by Cox et al because Cheo et al teach it is within the ordinary skill in the art to perform recombination reactions *in vivo* in bacterial cells and Cox et al teach the use of flp recombinase activity encoded by a plasmid to mediate site-specific recombination reactions *in vivo* in bacterial cells.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to regulate flp-mediated recombination events virtually anywhere in the bacterial chromosome as taught by Cox et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 2-5, 8, 11, 14 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ow (US Patent Application Publication No. 2002/0123145, cited in a prior action; see the entire reference) in view of Schlake et al (Biochemistry, Vol. 33, pages 12746-12751, 1994, cited in a prior action; see the entire reference). This is a new rejection, necessitated by Applicant's amendment to the claims in the reply filed 11/29/2005.

Ow teaches the claimed first integration cassette, first target cassette and rec element. Ow teaches a first integration cassette (receptor construct) comprising a promoter operably linked to a first exchangeable reporter segment comprising a thymidine kinase (tk) coding region (scorable homeostatic reporter element) and a zeocin resistance coding region (exchangeable reporter gene), wherein the tk coding sequence is linked to a first recombinase recognition site (PP') at its 5' end and to a second recombinase recognition site at its 3' end (PP') (e.g. Figure 4). More generally, Ow teaches integration cassettes comprising a polynucleotide flanked by two irreversible recombination sites (IRSs), which are stably integrated into the genome of a host organism (e.g. paragraphs [0014] and [0042]). Because the cassettes do not comprise sequence homologous to a chromosome of the target organism, integration will be random. Ow teaches a

first target cassette (donor construct) comprising a third recombinase recognition site (BB'), capable of recognizing the first recognition site in the first integration cassette; a first target element (cDNA); and a fourth recombinase recognition site (BB'), capable of recognizing the second recombinase recognition site in the first integration cassette (e.g. Figure 4). More generally, Ow teaches target cassettes comprising a polynucleotide flanked by two irreversible complementary recombination sites (CIRSs) (e.g. paragraphs [0014] and [0042]). Ow teaches a rec element encoding a recombinase polypeptide capable of catalyzing a recombination reaction between IRS and CIRS, wherein introduction of the rec element and the first target cassette to the recombinant cell population comprising the first integration cassette results in site-specific substitution of the first exchangeable reporter segment with the first exchangeable target segment (e.g. Figure 4, paragraphs [0014], [0037] and [0054]). Ow teaches that the rec element (polynucleotide encoding the recombinase) can be included in the first integration cassette (receptor construct) containing the IRSs (e.g. paragraphs [0045] and [0054]). Ow teaches that the rec element can be included in the first target cassette (donor construct) containing the CIRSs (e.g. paragraph [0054]). Ow teaches the use of the abovementioned system in host cells such as mammalian cells, fungi and bacteria. Ow teaches a first target element further comprising a first target gene and a first selectable marker gene (e.g. paragraphs [0060] and [0180]).

Ow does not teach a second integration cassette comprising fifth and sixth recombination sites and a second target cassette comprising seventh and eighth recombination sites capable of recognizing the fifth and sixth recombination sites, respectively, when the rec element encodes flp recombinase.

Schlake et al teach reciprocal exchange of DNA flanked by frt sites, where sets of target sites were engineered to enable two independent recombination events in a single enzymatic reaction (e.g. page 12748, The Concept; Figure 2). Further, Schlake et al teach pairs of FRTs that can mediate independent recombination events with an identical partner such as F + F_5 and F_2 + F_3 (e.g. page 12750, left column, 1st full paragraph; Table I). Schlake et al teach that the scope of rearrangements including insertion, excision, inversion and translocation can be extended considerably by the simultaneous use of wild-type and differentially mutated FRTs (e.g. page 12746, paragraph bridging columns). Schlake et al exemplify the use of the recombination sites flanking neomycin and Hyg Tk markers (e.g. Figure 1). Moreover, Schlake et al teach plasmid pOG44, which encodes flp recombinase protein (e.g. page 12747, Recombination Subsequent to Integration (Stable State)).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Ow to include the pairs of frt sites taught by Schlake et al because Ow and Schlake et al teach it is within the ordinary skill in the art to use different sets of recombining sites to mediate double-crossover events.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to select pairs of frt sites that can mediate independent recombination events with an identical partner using a single recombinase as taught by Schlake et al. Further, one would be motivated to use a second integration cassette and second targeting cassette containing a different pair of recombining sites both recognized by flp recombinase in that one would be able to perform additional double-crossover reactions without involving the tedious procedure and additional screening steps of using recombination sites recognized by a

second recombinase as taught by Schlake et al (e.g. page 12751, left column, 1st full paragraph). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments

Applicant's arguments (pages 21-25) filed 11/29/2005 have been fully considered but they are not persuasive.

The response asserts that Cheo does not teach an integration cassette in that Cheo does not teach that the promoter is located outside the recombination site. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the promoter being located outside the recombination site) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). As written, the claims require the integration cassette to comprise a first promoter and a homeostatic reporter element flanked at its 5' and 3' ends with recombinase recognition sites. The claims do not specify the location of the promoter relative to the 5' recombination site or 3' recombination site flanking the "at least one scorable homeostatic reporter element." Although the claims require the recombination sites to be linked to the recombinase recognition sites, the broadest reasonable interpretation of the term "linked" encompasses embodiments where the recombination sites are not directly linked but are linked by intervening sequence (e.g. a promoter).

The response asserts that the vectors taught by Cheo randomly integrate into the genome by non-homologous recombination, which is associated with numerous problems. This is not found persuasive because the claims are drawn to vectors that are capable of stable and random insertion. Thus, the claims read on the teachings of Cheo et al.

The response asserts that Cheo et al does not teach the cellular expression system of claim 11 in that Cheo teaches replacement of one or more nucleic acids by recombination with a different nucleic acid. Claim 11 reads on the teachings of Cheo et al for the reasons set forth above. For example, Figure 7 depicts a first integration cassette recombining with a first target cassette and a second integration cassette recombining with a second target cassette in the presence of a recombinase.

The response asserts that the additional references cited by the Examiner do not cure the deficiencies in the Cheo reference in that the additional references do not teach the claimed integration cassette. This is not found persuasive for the reasons set forth above. The additional references cited by the Examiner cure the deficiency of the Cheo reference with regard to the rec element encoding the at least one recombinase activity. Each of the other claimed elements are met by the teachings of Cheo et al.

For these reasons, and the reasons made of record in the previous office actions, the rejections are maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR, http://pair-direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's

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Jennifer Dunston
Examiner
Art Unit 1636

jad

CELIAN QIAN
PATENT EXAMINER